CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074927

Trade Name : ETODOLAC TABLETS 400MG

Generic Name: Etodolac Tablets 400mg

Sponsor : Applied Analytical Laboratories, Inc.

Approval Date: October 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074927

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074927

APPROVAL LETTER

ANDA 74-927

OCT 30 1997

Applied Analytical Laboratories, Inc.
Attention: Jeffrey S. Bauer, Ph.D.
U.S. Agent for: Aesgen Inc.
5051 New Centre Drive
Suite 103
Wilmington, NC 28403

Dear Sir:

This is in reference to your abbreviated new drug application dated July 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Tablets, 400 mg.

Reference is also made to your amendments dated April 29, June 6, July 25, August 4, August 7, and October 15, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Tablets, 400 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lodine® Tablets, 400 mg of Wyeth Ayerst Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

10/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074927

FINAL PRINTED LABELING

Each tablet contains 400 mg etodolac.
USUAL DOSAGE: See package circular for full prescribing information.
Store at 15°C - 30°C (59°F - 86°F). Dispense in a light-resistant container.

Manufactured for:
Aesgen INC.
Wilmington, NC 28403
By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

500 Tablets

CAUTION: Federal law prohibits dispensing without prescription.

4

ETODOLAC Tablets

400 mg

NDC 55370-547-08

LOT #:

EXP. DATE:

6235501MV

Revised 05/97

N 3 55370-547-08 3

Each tablet contains 400 mg etodolac.
USUAL DOSAGE: See package circular for full prescribing information.
Store at 15°C - 30°C (59°F - 86°F).
Dispense in a light-resistant container.

Manufactured for:
Aesgen INC.
Wilmington, NC 28403
By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

OCT 30 1997

100 Tablets

CAUTION: Federal law prohibits dispensing without prescription.

4

ETODOLAC Tablets

400 mg

NDC 55370-547-07

LOT #:

EXP. DATE:

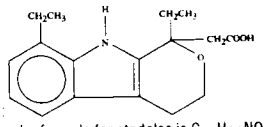
6235401MV

Revised 05/97

N 3 55370-547-07 6

DESCRIPTION

Etodolac (etodolac tablets) is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1acetic acid. The structural formula for etodolac is shown below:



The molecular formula for etodolac is $C_{17}H_{21}NO_3$. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol: water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

Etodolac tablets, for oral administration contain 400 mg of etodolac. In addition, the tablets contain the following inactive ingredients: hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Pharmacology

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis. Etodolac is a racemic mixture of [-]R- and [+]S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+]S-form is biologically active. Both enantiomers are stable and there is no [-]R to [+]S conversion *in vivo*.

Pharmacodynamics

Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see **CLINICAL PHARMACOLOGY, Clinical Trials).**

Pharmacokinetics

The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption

Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (± 1 SD) peak plasma concentrations range from approximately 14 ± 4 to 37 ± 9 mcg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1.
Etodolac Steady-State Pharmacokinetic Parameters
(N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability) [F]	≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V_{ss}/F]	362 ± 129 mL/kg
Distribution half-life [$t_{1/2,\ \alpha}$]	0.71 ± 0.5 h
Terminal half-life [$t_{1/2,\ \beta}$]	7.3 ± 4 h

Antacid Effects

The extent of absorption of etodolac is not affected when

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Antacid Effects
The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.
Food Effects
The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.
Distribution
Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.
Metabolism
Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.
Protein Binding
Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.
Elimination
The mean plasma clearance of etodolac, following oral dosing is 47 (± 16) mL/h/kg, and terminal disposition half-life is 7.3 (± 4) hours.
Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

-etodolac, unchanged	1%
-etodolac glucuronide	13%
-hydroxylated metabolites (6-, 7-, and 8-OH)	5%
-hydroxylated metabolite glucuronides	20%
-unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.
Special Populations
Elderly Patients
In clinical studies, etodolac clearance was reduced by about 15% in older patients (>65 years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment however, on the basis of body size (see **PRECAUTIONS-Geriatric Population**), as they may be more sensitive to antiprostaglandin effects than younger patients (see **PRECAUTIONS- Geriatric Population**).
Renal Impairment
Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.
Hepatic Impairment
In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.
Clinical Trials
Analgesia
Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Etodolac 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Etodolac 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required [illegible] medications.
The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.
INDICATIONS AND USAGE
Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.
CONTRAINDICATIONS
Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac [illegible]
In patients [illegible]

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INDICATIONS AND USAGE

Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.

CONTRAINDICATIONS

Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see **WARNINGS—Anaphylactoid Reactions**).

WARNINGS

Risk of Gastrointestinal (GI) Ulceration, Bleeding, and Perforation with Nonsteroidal, Anti- Inflammatory Drug (NSAID) Therapy

Serious GI toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers gross bleeding or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Anaphylactoid Reactions

Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see **CONTRAINDICATIONS** and **PRECAUTIONS—General Precautions**, Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

In cases with advanced kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see **PRECAUTIONS—General Precautions**, Renal Effects).

Pregnancy

In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see **PRECAUTIONS—Pregnancy**, Teratogenic Effects—Pregnancy Category C).

PRECAUTIONS

General Precautions

Renal Effects

As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with

relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

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A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **ADVERSE REACTIONS**) may be attributable to these metabolites should be considered.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), etodolac should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema

Fluid retention and edema have been observed in some

patients taking NSAIDS, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma

About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Information for Patients

Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etodolac should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see **WARNINGS—Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal Anti-Inflammatory Therapy**).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see **WARNINGS**).

Laboratory Tests

Patients on long-term treatment with etodolac as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g. eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

Drug Interactions

Antacids

The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

Aspirin

When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

Warfarin

Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

Cyclosporine, Digoxin, Lithium, Methotrexate

Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

Phenylbutazone

Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

Drug/Laboratory Test Interactions

The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/m² [illegible]

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Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2 respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 mcg/mL) compared to negative controls (2%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

Pregnancy

Teratogenic Effects—Pregnancy Category C

In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.

Labor and Delivery

In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Population

As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of etodolac were seen compared with the general population (see **CLINICAL PHARMACOLOGY—Pharmacokinetics**.)

ADVERSE REACTIONS

Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg/day).

Incidence Greater Than or Equal to 1% - Probably Causally Related

Body as a whole—Chills and fever.

Digestive system—Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.

Nervous system—Asthenia/malaise*, dizziness*, depression, nervousness.

Skin and appendages—Pruritus, rash.

Special senses—Blurred vision, tinnitus.

Urogenital system—Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient [illegible]

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Skin and appendages—Pruritus, rash.

Special senses—Blurred vision, tinnitus.

Urogenital system—Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked.

Incidence Less Than 1% - Probably Causally Related (*Adverse reactions reported only in worldwide* postmarketing experience, not seen in clinical trials, are considered rarer and are italicized)

Body as a whole—*Allergic reaction, anaphylactoid reaction.*

Cardiovascular system—Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive system—Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*

Hemic and Lymphatic system—Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*

Metabolic and nutritional—Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*

Nervous system—Insomnia, somnolence.

Respiratory system—Asthma.

Skin and appendages—Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome,* hyperpigmentation, *erythema multiforme.*

Special senses—Photophobia, transient visual disturbances.

Urogenital system—*Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.*

Incidence Less Than 1% - Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians)

Body as a whole—Infection, headache.

Cardiovascular system—Arrhythmias, *myocardial infarction,* cerebrovascular accident.

Digestive system—Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and nutritional—Change in weight.

Nervous system—Paresthesia, confusion.

Respiratory system—Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and appendages—Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special senses—Conjunctivitis, deafness, taste perversion.

Urogenital system—Cystitis, *hematuria, leukorrhea,* renal calculus, interstitial nephritis, uterine bleeding irregularities.

OVERDOSAGE

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

DOSAGE AND ADMINISTRATION

As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function. (see **PRECAUTIONS – General Precautions,** Renal Effects).

Analgesia

The recommended total daily dose of etodolac for acute pain is up to 1000 mg given as 200-400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risk, the dose may be increased to 1200 mg/day in

8

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Analgesia

The recommended total daily dose of etodolac for acute pain is up to 1000 mg given as 200-400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks; the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

Osteoarthritis

The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED

Etodolac is available as:

Etodolac Tablets
400 mg tablets (white, elliptical shaped, unscored tablet, debossed with "A04" on one side and "400" on the other)
—in bottles of 100, NDC 55370-547-07
—in bottles of 500, NDC 55370-547-08

Store at 15°C-30°C (59°F-86°F).
Store tablets in original container until ready to use.
Dispense in a light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Manufactured for:

Aesgen INC.

by:
MOVA PHARMACEUTICAL CORPORATION
Caguas, PR 00725, USA

Item #634701MV
Rev 07/97

MOVA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074927

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-927

3. NAME AND ADDRESS OF APPLICANT
Aesgen Inc.
Attention: Jeffrey S. Bauer
5051 New Centre Drive
Suite 103
Wilmington, NC 28403

4. LEGAL BASIS FOR SUBMISSION
Listed Drug Product: Lodine® Tablets (Etodolac Tablets), 400 mg
Patent # 4,076,831 Wyeth Ayerst, expires February 28, 1997.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Etodolac Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original Application submitted, July 15, 1996.
Refuse to File letter, September 13, 1996 (regarding English translation of documents
Teleconference between J. Phillips and Aesgen, September 26, 1996
The Firm,s reply to Teleconference, September 30, 1996.
Correction to Refuse to File Letter, October 11, 1996.
Minor Amendment, April 11, 1997.
Minor Amendment, June 6, 1997 (This Review).
August 4, 1997.

10. PHARMACOLOGICAL CATEGORY
Antiinflammatory (NSAID)

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Innovator's NDA # 18922

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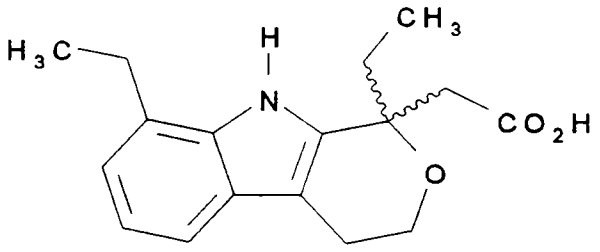
13. DOSAGE FORM
Tablet

14. POTENCY
400 mg

15. CHEMICAL NAME AND STRUCTURE

Etodolac

$C_{17}H_{21}NO_3$; M.W. = 287.36



1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic acid.
CAS [41340-25-4]

16. RECORDS AND REPORTS N/A

17. COMMENTS
In the last deficiency letter dated May 14, 1997, the firm was requested to revise its impurities specification to include limits for individual known and unknown impurities and include these in its specification for the drug product release and stability. **In response to this deficiency, the firm provided revised specification for the individual unknown impurities but not for the individual known impurities.**

Following a Tcon. between Jim Wilson and Vilayat Sayeed, and the firm, the firm submitted a Facsimile Amendment on August 4, 1997 which addressed the issue of the bulk product release and stability impurities specifications, and dissolution specifications for the drug product.

See review sections 28 and 29 for firm's revised specifications.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER:
U.S. Atwal

DATE COMPLETED:
June 18, 1997

DATE REVISED:
September 3, 1997

cc: ANDA 74-927
DUP Jacket
Division File
Field Copy

Endorsements:
HFD-623/U. Atwal, Ph.D./ 9/9/97
HFD-623/V. Sayeed, Ph.D./ 9/9/97
X:\NEW\FIRMSAM\AESGEN\LTRS&REV\74927.RV3
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074927

BIOEQUIVALENCE REVIEW(S)

OCT 30 1997

Etodolac
400 mg Tablets
ANDA #**74-927**
Reviewer: Z.Z. Wahba
File #74927a2.097

Aesgen, Inc.
Wilmington, NC
Submission Date:
October 15, 1997
Oct 25, 1997

AMENDMENT TO A REVIEWED IN-VIVO BIOEQUIVALENCE STUDY AND IN VITRO DISSOLUTION TESTING DATA

BACKGROUND:

1. On 10/14/97, the firm sent a facsimile letter including additional dissolution data, comparing its 400 mg Etodolac Tablets to the reference drug product Lodine® 400 mg Tablets (Wyeth-Ayerst).

2. The firm has conducted an in vivo bioequivalence study (under fasting and non-fasting conditions) which has been found acceptable.

3. The firm was asked to conduct dissolution profile testing for the test product applying the following specifications: The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 at 37°C using USP 23 apparatus I (Basket) at 100 rpm at the time points 10, 15, 20 and 30 minutes. The results of the dissolution profile testing are presented in the following dissolution section:

DISSOLUTION:

Method:	USP 23 apparatus II (Basket) at 100 rpm
Medium:	1000 mL of pH 7.5 phosphate buffer
Number of Units:	12 Tablets
Test products:	Aesgen's Etodolac 400 mg Tablets, lot #MNT0141
Reference products:	Wyeth-Ayerst's Lodine® 400 mg Tablets, lot #9951194
Specifications:	NLT ____ in 30 minutes.

Dissolution testing results are shown in the following Table.

Table. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Tablets
Dose Strength: 400 mg
ANDA No.: 74-927
Firm: Aesgen, Inc.
Submission Date: July 15, 1996, Facsimile letter dated 10/15/97
File Name: 74927a2.097

I. Conditions for Dissolution Testing:

USP XXII Basket:X Paddle: RPM: 100
No. Units Tested: 12 Tablets
Medium: 1000 mL of phosphate buffer pH 7.5
Specifications: NLT [redacted] in 30 minutes
Reference Drug: Wyeth-Ayerst's Lodine®

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MNT0141 Strength(mg) 400			Reference Product Lot # 9951194 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
5	35	[redacted]	17.9	41	[redacted]	16.3
10	76	[redacted]	7.8	85	[redacted]	4.8
20	99	[redacted]	1.2	101	[redacted]	0.8
30	100	[redacted]	1.2	101	[redacted]	0.9
45	100	[redacted]	1.2	100	[redacted]	0.9

The dissolution data for the test product is acceptable.

RECOMMENDATION

1. The two bioequivalence studies conducted by Aesgen, Inc., under fasting and non-fasting conditions on its drug product, Etodolac Tablet 400 mg (lot #MNT0141), comparing it to Wyeth-Ayerst's Lodine® Tablet 400 mg have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Aesgen's Etodolac Tablet 400 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Tablet 400 mg.

2. The dissolution testing conducted by the firm on its Etodolac Tablets, 400 mg (lot #MNT0141) has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution

testing should be conducted in 1000 mL of phosphate buffer pH 7.5 at 37°C using USP 23 apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Not less than____ of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendation.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE ____ 10/29/97

Concur: _____ Date: 10/30/97
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #74-927, (original, duplicate), HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/102797/wp #74927a2.o97

DW

ANDA 74-927

Aesgen, Inc.
Attention: Jeffrey S. Bauer
5051 New Centre Drive
Suite 103
Wilmington NC 28403

JUN 30 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etodolac Tablets, 400 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 at 37°C using USP 23 apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

   > Not less than_____(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 25 1997

Etodolac
400 mg Tablets
ANDA #**74-927**
Reviewer: Z.Z. Wahba
File #74927a.497

Aesgen, Inc.
Wilmington, NC
Submission Date:
April 29, 1997

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY AND DISSOLUTION DATA (Dated January 02, 1997)

BACKGROUND

The firm has previously submitted two in vivo bioequivalence studies (single-dose fasting and single-dose post-prandial) comparing its test drug product, Aesgen's 400 mg Etodolac Tablets to the reference listed product, Wyeth-Ayerst's Lodine® 400mg Tablets.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (the review dated January 02, 1997, ANDA #74-927) due to problems cited in the deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Deficiency Comment #A.1

A. Under Fasting Condition (Clinical project #P95-346)

1.i. The raw data on the floppy diskette do not match the data in the submission (hard copy data).
Resubmit the correct data on both hard copy and floppy diskette as well as the outcome of the statistical analysis.

The firm's response to comment #A.1.i

A diskette containing the raw data for study #P95-346 under fasting conditions and study 095-347 under non-fasting conditions was submitted. A hard copy of the data was also provided (see the firm's correspondence on April 29, 1997; Exhibit #1 for study #P95-346 and as Exhibit #2 for study #P95-347).

The firm's response to comment #A.1.i is acceptable.

Deficiency Comment #A.1.ii

The raw data on the floppy diskette should include the plasma levels and pharmacokinetics parameters (AUCt, AUCi, Cmax, Tmax, T1/2, and

Kel) for all subjects.

The firm's response to Comment #A.1.ii

A diskette that contains the requested information was provided. Also see the In Vivo Bioequivalence Study and Statistical Analysis section in this report.

The firm's response to comment #A.1.ii is acceptable.

Deficiency Comment #A.1.iii

Include an example(s) of the method of calculation of plasma samples.

The firm's response to Comment #A.1.iii

The firm's response to comment #A.1.iii is acceptable.

Deficiency Comment #2

On pages 525-526, Mayo's Lab letter (second paragraph) mentions that the results of the plasma concentrations of etodolac are attached as appendices 1, 2, 3 and 4. The appendices that were provided do not match what was mentioned in the letter. Please provide the missing information.

The firm's response to comment #2

The initial report submitted stated that the results of the plasma concentrations were attached as Appendices 1, 2, 3 and 4. The tables contained in the report, however, did not contain the Appendix identifiers. Copies of these tables with the identifiers for the two etodolac 400 mg studies are provided as Exhibit #4 for study #P95-346 and as Exhibit #5 for study #P95-347.

The firm's response to comment #2 is acceptable.

Deficiency Comment #3

The firm's response to Comment #3

The firm's response to comment #3 is acceptable.

Deficiency Comment #4

The firm's response to Comment #4

The firm's response to comment #4 is acceptable.

Deficiency comment #5

The firm's response to Comment #5

The firm's response to comment #5 is acceptable.

Deficiency comment #6

Provide the dates of the beginning and end of the analytical assay of the plasma samples.

The firm's response to Comment #6

The analytical assay for the etodolac 400 mg Fasting Study was started on March 20, 1996, and completed on April 5, 1996.

The firm's response to comment #6 is acceptable.

Deficiency comment #7

Provide the concentration of the internal standard that was used for assay recovery data.

The firm's response to Comment #7

The concentration of the internal standard used in the etodolac assay was

The firm's response to comment #7 is acceptable.

Deficiency comment #8

Provide the batch/lot size for the test product.

The firm's response to Comment #8

The batch size for the test product was _____ equivalent to _____ tablets. The actual yield of coated tablets produced for the test batch was _____

The firm's response to comment #8 is acceptable.

Deficiency comment #B1

Under Non-Fasting Conditions (Clinical project NP95-347):
The firm provided raw data on the floppy diskette do not match the data in the submission (hard copy data).

i. The firm is requested to resubmit the right data on both hard copy and floppy diskette as well as the outcome of the statistical analysis.
ii. The raw data on the floppy diskette should include the plasma levels and pharmacokinetics parameters (AUCt, AUCi, Cmax, Tmax, T1/2 and Kel) for all subjects.

The firm's response to Comment #B.1

The response to comments A.1.(i) and (ii) also apply to comments B.1.(i) and (ii). A diskette that contains the requested information was provided. Also see the **In Vivo Bioequivalence Study and Statistical Analysis** section in this report.

The firm's response to comment #B1 is acceptable.

Deficiency comment #B.2

The firm's response to Comment #B.2

The firm's response to comment #B.2 is acceptable.

Deficiency comment #C

The application provides two comparative formulation tables on pages 1572 and 1596. The tables show that the amount (in mg) of each ingredient per tablet is the same in both tables, however, based on %W/W values they are different. Please provide clarification for these differences.

The firm's response to Comment #C

The firm's response to comment #C is acceptable.

In Vivo BE Study and Statistical Analysis (Under Fasting Conditions)

Twenty-eight (24 plus 4 alternates) healthy male subjects were enrolled and completed the study (subjects #1-28). All subjects received a single oral dose of 400 mg etodolac on two periods separated by one week.

The pharmacokinetic parameters of etodolac were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters of the level of plasma concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the tables below:

Table 1
Mean Plasma Concentrations (µg/mL) of Etodolac in 28 Subjects Following a Single Oral Dose of 400 mg Etodolac Under Fasting Conditions (Test Lot#MNT0141, Ref. Lot #9951194)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.01	0.05	0.00	0.00	.
0.25	1.71	1.86	4.75	6.33	0.36
0.5	9.99	7.79	16.53	10.37	0.60
0.75	16.22	10.00	19.14	10.08	0.85
1	19.13	10.18	19.19	8.46	1.00
1.33	18.66	7.63	19.63	8.23	0.95
1.67	18.09	6.43	19.11	6.32	0.95
2	17.97	5.63	17.83	5.06	1.01
2.5	16.68	5.75	16.18	3.51	1.03
3	14.56	4.59	14.71	4.33	0.99
4	10.92	2.94	11.18	3.00	0.98
6	5.85	2.30	5.45	1.08	1.07
8	4.37	1.38	4.08	0.91	1.07
12	2.75	0.71	2.62	0.54	1.05
16	1.66	0.51	1.56	0.38	1.06
24	0.82	0.27	0.77	0.24	1.06
30	0.42	0.22	0.37	0.21	1.12
36	0.22	0.20	0.18	0.19	1.20

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table 2
Mean Pharmacokinetic Parameters in 28 Subjects Following a Single Oral Dose of 400 mg Etodolac Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	126.22	20.62	126.56	20.11	1.00
AUCT	122.19	19.81	122.53	19.92	1.00
CMAX	26.55	5.40	27.49	6.52	0.97
KE	0.10	0.02	0.10	0.02	0.97
*LAUCI	124.58	0.17	124.98	0.16	1.00
*LAUCT	120.63	0.16	120.93	0.17	1.00
*LCMAX	26.02	0.21	26.84	0.22	0.97
THALF	7.45	1.63	7.30	1.75	1.02
TMAX	1.64	1.10	1.43	0.81	1.15

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio
* The values represent the geometric means (antilog of the means of the logs).

Table 3
LSMeans And The 90% Confidence Intervals (Under Fasting Conditions)

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCI	126.22	126.56	96.74	102.72
AUCT	122.19	122.53	96.79	102.67
CMAX	26.55	27.49	89.46	103.71
*LAUCI	124.58	124.98	96.71	102.74
*LAUCT	120.63	120.93	96.84	102.76
*LCMAX	26.02	26.84	90.34	103.99

UNIT: AUC=μG HR/ML CMAX=μG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
* The values represent the LSMEANS (antilog of the means of the logs).

1. The mean plasma etodolac levels reached a maximum level of concentration around 1.0-1.33 hours (Table #1 and Figures #1 and 2).

2. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3). The geometric T/R mean ratios (RMEAN12) for AUCt, AUCi and Cmax were within the acceptable range of 0.8-1.25 (Table #2).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUCt and AUCi.

For the Cmax, there was no significant treatment effect of the test and reference drug treatments. However, there was a significant sequence and period effects (p less than 0.05) for the log-transformed pharmacokinetic parameter Cmax.

3. The arithmetic T/R mean ratios for Tmax, Kel and T1/2 were 1.15, 0.97 and 1.02, respectively (Table #2). The percentage of change of the T/R mean for the Tmax, Kel and T1/2 are acceptable.

In Vivo BE Study and Statistical Analysis (Under Non-Fasting Conditions)

Eighteen (18) healthy male subjects were enrolled and completed the study (subjects #1-18). All subjects received a single oral dose of 400 mg etodolac on two periods separated by one week.

The pharmacokinetic parameters of etodolac were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters of the level of plasma concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the tables below:

Table 4
Mean Plasma Concentrations of Etodolac (µg/mL) in 18 Subjects Following 400 mg Oral Doses of Etodolac Under Non-Fasting Conditions (Test Lot#MNT0141, Ref. Lot #9951194)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	1.74	2.37	0.20	0.42	0.58	1.15	8.88
0.5	7.71	5.98	2.57	4.13	2.87	4.33	3.00
0.75	13.37	8.58	5.62	6.49	5.97	6.62	2.38
1	16.64	8.47	9.49	7.72	11.14	8.89	1.75
1.33	19.04	7.03	12.22	7.49	15.23	7.28	1.56
1.67	18.23	5.68	13.34	5.21	14.67	5.86	1.37
2	16.58	4.48	14.95	5.76	13.68	3.23	1.11
2.5	14.82	3.55	13.07	4.28	12.68	2.90	1.13
3	13.36	3.49	11.75	3.32	11.45	2.14	1.14
4	10.34	2.84	10.43	2.73	10.18	2.26	0.99
6	5.46	1.17	7.24	1.73	7.66	1.77	0.75
8	3.98	0.93	4.35	1.02	4.29	0.76	0.92
12	2.37	0.66	2.63	0.67	2.54	0.71	0.90
16	1.53	0.48	1.59	0.53	1.58	0.57	0.96
24	0.79	0.33	0.85	0.35	0.79	0.36	0.92

30	0.41	0.33	0.43	0.31	0.35	0.34	0.95
36	0.23	0.29	0.25	0.21	0.16	0.26	0.91

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	2.99	0.34
0.5	2.69	0.90
0.75	2.24	0.94
1	1.49	0.85
1.33	1.25	0.80
1.67	1.24	0.91
2	1.21	1.09
2.5	1.17	1.03
3	1.17	1.03
4	1.02	1.02
6	0.71	0.95
8	0.93	1.01
12	0.93	1.03
16	0.97	1.01
24	0.99	1.07
30	1.17	1.23
36	1.41	1.54

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=μG/ML TIME=HRS

Table 5
Mean Pharmacokinetic Parameters in 18 Subjects Following a Single Oral Dose of 400 mg Etodolac Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	117.69	23.74	111.41	22.25	111.38	23.43	1.06
AUCT	112.43	21.32	107.09	21.32	106.35	21.71	1.05
CMAX	23.47	4.92	18.64	5.48	19.96	5.38	1.26
KE	0.09	0.02	0.09	0.02	0.10	0.02	0.97
*LAUCI	115.40	0.21	109.28	0.20	109.12	0.21	1.06
*LAUCT	110.42	0.20	105.04	0.20	104.30	0.20	1.05
*LCMAX	22.98	0.21	17.81	0.32	19.27	0.27	1.29
THALF	8.04	2.41	7.71	1.67	7.12	1.75	1.04
TMAX	1.56	0.69	1.96	1.05	1.83	0.93	0.80

(CONTINUED)

	RMEAN13	RMEAN23

PARAMETER		
AUCI	1.06	1.00
AUCT	1.06	1.01
CMAX	1.18	0.93
KE	0.89	0.92
*LAUCI	1.06	1.00
*LAUCT	1.06	1.01
*LCMAX	1.19	0.92
THALF	1.13	1.08
TMAX	0.85	1.07

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=μG HR/ML CMAX=μG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 6
Test/Reference Products Ratios for Pharmacokinetic Parameters for Individual Subjects (Under Non-Fasting Conditions)

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	117.69	111.41	111.38	1.06	1.06	1.00
AUCT	112.43	107.09	106.35	1.05	1.06	1.01
CMAX	23.47	18.64	19.96	1.26	1.18	0.93
*LAUCI	115.40	109.28	109.12	1.06	1.06	1.00
*LAUCT	110.42	105.04	104.30	1.05	1.06	1.01
*LCMAX	22.98	17.81	19.27	1.29	1.19	0.92

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=μG HR/ML CMAX=μG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma etodolac levels reached the maximum around 1.33-2.0 hours (Table #4 and Figures #3 and #4).

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi and Cmax were all within the acceptable range of 0.8 to 1.25 (Table #5).

DISSOLUTION:

Method: USP 23 apparatus II (Paddles) at 50 rpm
Medium: 900 mL of pH 7.5 phosphate buffer
Number of Units: 12 Tablets

Test products: Aesgen's Etodolac 400 mg Tablets, lot #MNT0141
Reference products: Wyeth-Ayerst's Lodine® 400mg Tablets, lot #9951194
Specifications: NLT ____ in 30 minutes.
Method: FDA method

Dissolution testing results are shown in Table #7.

Table 7. In Vitro Dissolution Testing

Drug (Generic Name): Etodolac Tablets
Dose Strength: 400 mg
ANDA No.: 74-927
Firm: Aesgen, Inc.
Submission Date: July 15, 1996
File Name: 74927sd.796

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:X RPM: 50
No. Units Tested: 12 Tablets
Medium: 900 mL of phosphate buffer pH 7.5
Specifications: NLT ____ in 30 minutes
Reference Drug: Wyeth-Ayerst's Lodine®
Assay Methodology: ____

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MNT0141 Strength(mg) 400			Reference Product Lot # 9951194 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
15	82.9		7.5	77.7		14.1
30	98.1		1.7	98.3		1.7
45	98.8		1.3	99.1		1.5
60	98.8		1.6	99.8		1.3

Comments on the Dissolution Data:

a. The USP 23 has no dissolution requirements for etodolac.

b. The in vitro dissolution testing submitted by the firm on its Etodolac 200 mg and 300 mg tablets is acceptable.

c. The dissolution data of the reference product exhibited lower mean values of dissolution than the test product at 15 minutes dissolution time point.

REVIEWER'S COMMENTS

1. In this amendment the firm has provided satisfactory responses to all the deficiencies that were identified in the previous review

(reviewed date January 02, 1997).

2. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Aesgen's Etodolac Tablet 400 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Tablet 400 mg. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax were all within the acceptable range of 80-125%.

3. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Aesgen's Etodolac Tablet 400 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Tablet 400 mg. The ratios of the test mean to the reference mean for the AUCt, AUCi, Cmax were within the acceptable range of 0.8-1.25.

3. Dissolution Data: The firm has provided an acceptable comparative dissolution data for its drug product, Aesgen's Etodolac Tablets 400 mg and the reference product, Lodine® Tablets 400 mg. The firm conducted the dissolution test using FDA methodology.

SPECIAL COMMENT TO THE FIRM:

The firm is advised to conduct a dissolution profile testing for the test product applying the following specifications:
The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 at 37°C using USP 23 apparatus I (Basket) at 100 rpm at the time points 10, 15, 20 and 30 minutes.
The results of the dissolution profile testing should be submitted to the Office of Division of Bioequivalence.

RECOMMENDATION

1. The two bioequivalence studies conducted by Aesgen, Inc., under fasting and non-fasting conditions on its drug product, Etodolac Tablet 400 mg (lot #MNT0141), comparing it to Wyeth-Ayerst's Lodine® Tablet 400 mg have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Aesgen's Etodolac Tablet 400 mg is bioequivalent to the reference product, Wyeth-Ayerst's Lodine® Tablet 400 mg.

2. The dissolution testing conducted by the firm on its Etodolac Tablets, 400 mg (lot #MNT0141) has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of phosphate buffer pH 7.5 at 37°C using USP 23 apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

Not less than ____ of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations and the comment included above (in section "Special Comments to the Firm").

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 6/25/97

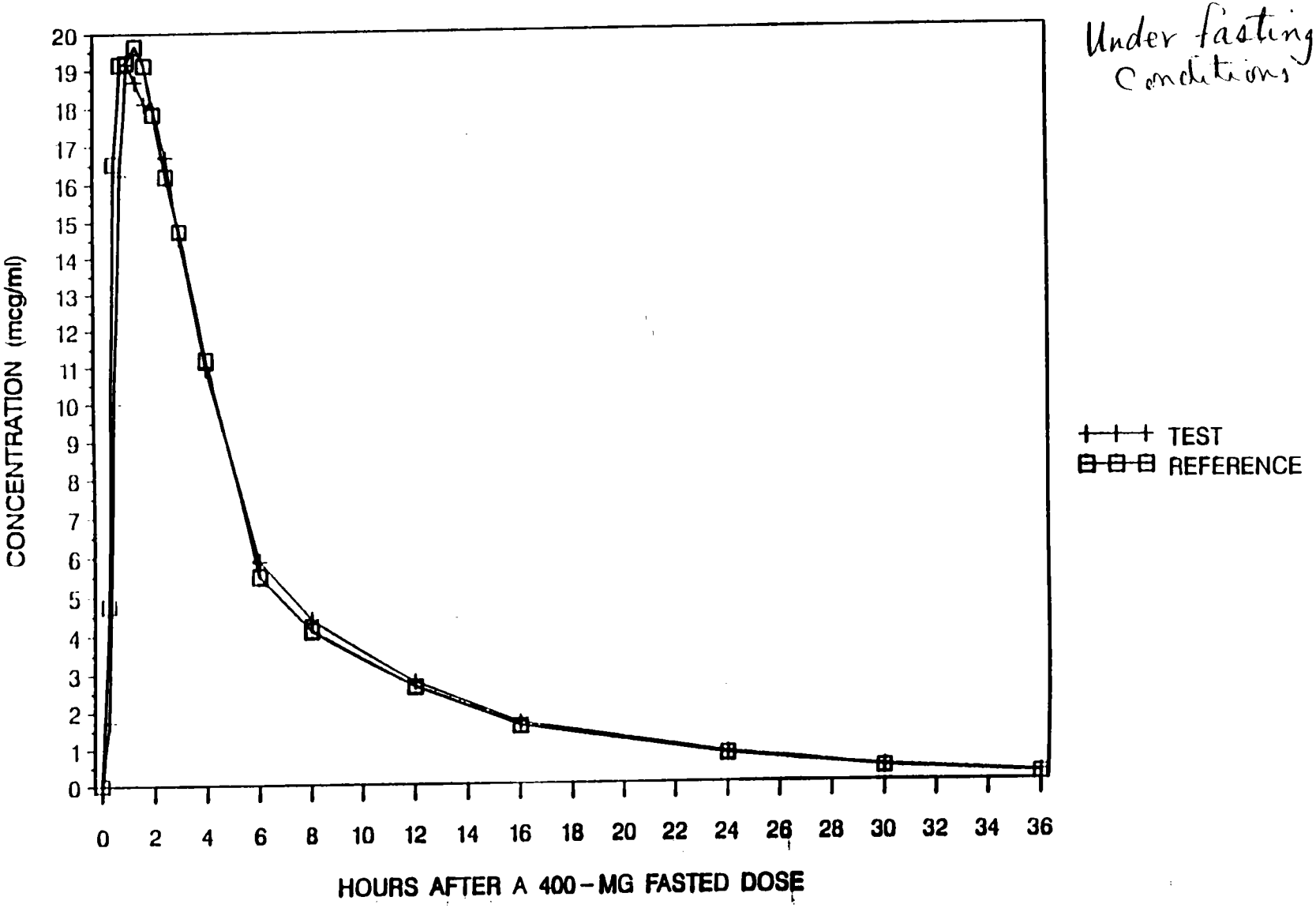
Concur: _____ Date: 6/25/97
fw Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 74-927 (original, duplicate), HFD-630, HFD-658 (Mhatre, Wahba), HFD-650 (Director), Drug File, Division File
ZZWahba/051997/061997/file #74877a.d96

Figure # 1
ANDA # 74-927

ETODOLAC 400 MG TABLET STUDY (PRACS 95-346; STATS ANALYSES 9631101S)

LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=28)



Under fasting conditions

Figure #
ANDA # 74-927

ETODOLAC 400 MG TABLET STUDY (PRACS 95-346; STATS ANALYSES 9631101S)

NATURAL LOG OF LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=28)

Under fasting conditions

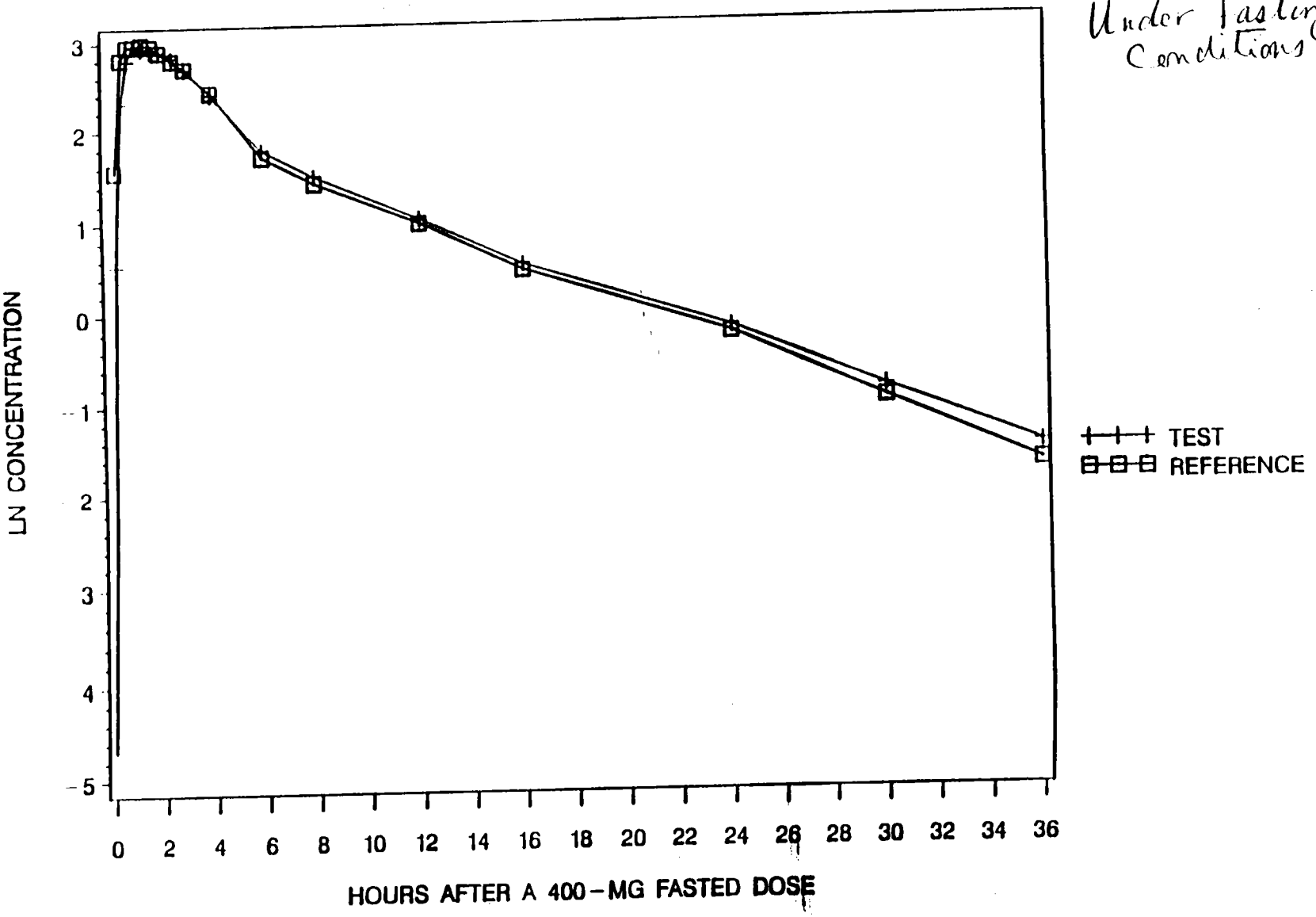


Figure #3

ANDA # 74927 (Under Non-Fasting Conditions)

ETODOLAC TABLET FOOD EFFECTS STUDY (PRACS P95-347; STATS ANALYSES 9631102S)

LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=18)

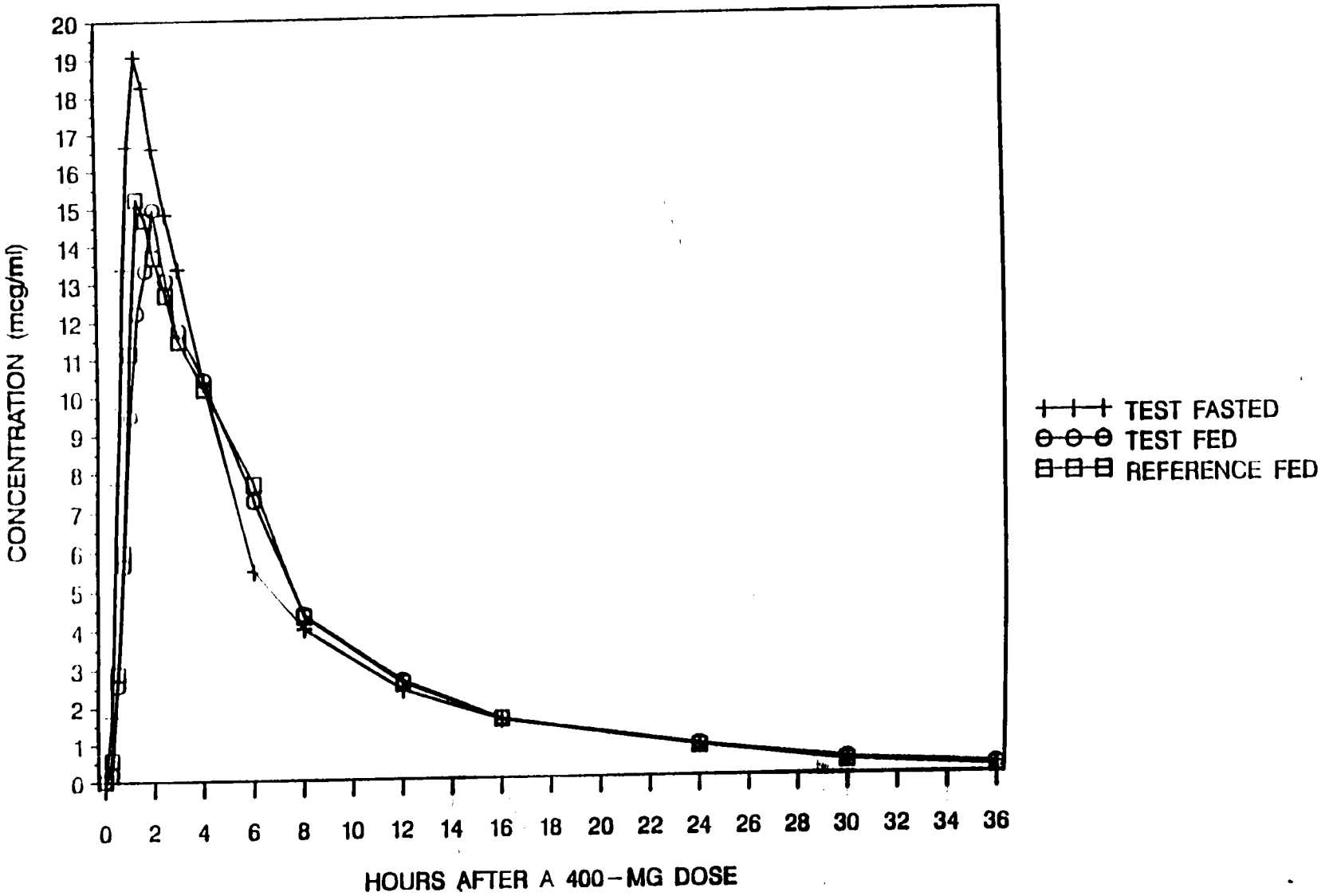


Figure # .

ANDA # 74-927 (Under Non-fasting Conditions)

ETODOLAC TABLET FOOD EFFECTS STUDY (PRACS P95-347; STATS ANALYSES 9631102S)
NATURAL LOG OF LEAST-SQUARES MEAN PLASMA ETODOLAC CONCENTRATIONS (N=18)